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(21) International Application Number: PCT/GB97/01586 (22) International Filing Date: 12 June 1997 (12.06.97) (30) Priority Data: 9612581.0 15 June 1996 (15.06.96) GB (71) Applicant (for all designated States except US): SMITH & NEPHEW PLC [GB/GB]; 2 Temple Place, Victoria Embankment, London WC2R 3BP (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): ALI, Saad, Aboul, Majeed [GB/GB]; 71 Yarbrough Way, York YO1 5HQ (GB). ROSE, John [GB/GB]; 3 St. Oswalds Close, Wilberfoss, York YO4 5LT (GB). SEARLE, Richard, John [GB/GB]; 12 Fairway Drive, Upper Poppleton, York YO2 6HE (GB). (74) Agent: SMITH & NEPHEW GROUP RESEARCH CENTRE; Group Patents & Trade Marks Dept., York Science Park, Heslington, York YO1 5DF (GB).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: BIODEGRADABLE LIQUID CRYSTALLINE POLYMERS (57) Abstract Novel thermotropic polymers, typically aromatic poly(ester-anhydride)s, having high modulus and biodegradability, have use as bone fixative materials and may be used in the construction of prosthetic devices and for filling other bone defects.		

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BIODEGRADABLE LIQUID CRYSTALLINE POLYMERS

This invention relates to novel polymers and particularly high performance bioresorbable polymers which have liquid crystalline properties.

Thermotropic polyesters are known and such materials generally possess advantageous properties such as, inter alia, high thermostability, low sensitivity to oxidation. However, such polyesters are generally not biodegradable.

Although many biodegradable polymers are known, such as those comprising lactic acid or β -hydroxybutyric, they are generally aliphatic in nature. Whilst they find utility in, for example, drug delivery systems or medical sutures, they do not possess the high strength and high modulus required for use in, eg. load bearing implants.

Polyester anhydrides are known from European Patent application No.0055527. However, the polyester anhydrides disclosed therein are not sufficiently bioresorbable or do not possess sufficient strength and/or modulus to be suitable as load bearing bioresorbable implants.

We have now surprisingly found a novel polymeric material which overcomes or mitigates these disadvantages.

Thus according to the invention we provide a polymeric material comprising repeating units of an aromatic mesogenic moiety, a hydrolysable moiety and a spacer moiety.

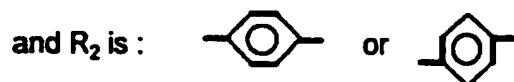
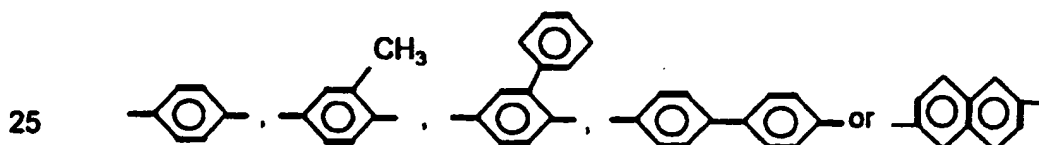
The polymeric material is preferably a condensation product containing aromatic ester moieties as the mesogenic component, mixed aromatic and aliphatic anhydride moieties as the hydrolysable component and aliphatic chains as the spacer moiety. Suitably these components may be provided by a condensation product comprising both aromatic and aliphatic diacid residues or functional derivatives thereof and residues of polyfunctional nucleophilic species such as a diol or thiol. Thus the preferred polymeric materials of the present invention are poly(ester-anhydride)s. Alternatively the mesogenic component may be derived from aromatic amide moieties.

The aromatic mesogenic moiety may be a polyester moiety and is preferably a condensation product of, for example, a terephthaloyl or isophthaloyl moiety and a quinoid such as hydroquinone, methylhydroquinone, phenylhydroquinone, biphenol or dihydroxynaphthalene or derivatives thereof.

Thus the aromatic mesogenic moiety aptly comprises a moiety of formula I.

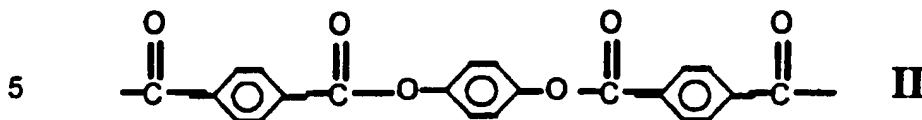


where R_1 is:



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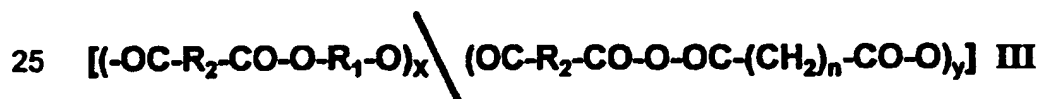
A preferred mesogenic moiety comprises a moiety of the general formula II



The hydrolysable moiety may comprise any conventionally known hydrolysable group. However, a preferred hydrolysable moiety is an anhydride linkage. Such anhydrides may be the condensation product of an aliphatic diacid derivative and an aromatic diacid derivative, such as a terephthaloyl acid derivative, eg. terephthaloyl chloride or an isophthaloyl derivative such as isophthaloyl chloride.

15 The spacer moiety is any inert group and may preferably comprise an aliphatic chain, for example comprising methylene groups from C₂ to C₂₀, suitably from C₂ to C₁₈, and preferably from C₄ to C₁₀. Alternatively, the spacer moiety may comprise alkylene oxide units ethylene oxide, propylene oxide or tetramethylene oxide units.

Thus according to the invention we provide a polymeric material comprising repeating units of formula III, →



in which:

n is an integer from 2 to 20, preferably from 2 to 16, more preferably 4 to 10,

30 R₁ and R₂ are as defined above and the ratio of x:y is from 1:99 to 99:1

In a preferred embodiment R_1 and R_2 is methyl-substitued phenyl.

5 According to a further feature of the invention we provide a method of manufacturing a polymeric material as hereinbefore described which comprises condensing a terephthaloyl or isophthaloyl compound and a quinoid such as hydroquinone, methylhydroquinone, phenylhydroquinone, biphenol or
10 dihydroxynaphthalene or derivatives thereof and an aliphatic diacid or derivative thereof.

The terephthaloyl or isophthaloyl derivative is preferably an acid halide, eg. acid chloride such as terephthaloyl or isophthaloyl
15 chloride. Such materials are generally commercially available.

The quinoid derivative is preferably an activated hydroquinone such as the silylated derivative, eg. bis-trimethylsilyl hydroquinone. Bis-trialkylsilyl hydroquinones may be manufactured by, inter alia,
20 reacting the respective quinoid with hexalkyldisilazane.

Similarly, the aliphatic diacid derivative is preferably an activated diacid such as a silylated diacid, eg. comprising silyl groups as hereinbefore described.

25

The polymeric material of the invention is advantageous in that it may be degradable to fragments of low molecular weight, which may in itself facilitate bioresorbability. Such polymeric materials may be processed to produce high strength and high modulus materials
30 which are useful in the manufacture of, inter alia, implantable devices, eg. implantable fixation devices such as bone fixation or

5

prosthetic devices. The desired strength and modulus of the polymeric materials of the invention is evidenced by the presence of liquid crystal properties.

5 Thus according to a further feature of the invention we provide a medical fixation device comprising a polymeric material as hereinbefore described.

10 We further provide the use of a polymeric material as hereinbefore described in the manufacture of a medical fixation device.

15 We also provide a method of bone fixation which comprises attaching a fixation device as hereinbefore described to portions of existing bone.

20 Aptly such fixation devices are preformed to the shape of implantable prosthetic devices, such as femoral head or condylar prostheses or as a filling material, which may be suitably shaped, to replace missing or excised bone portions.

The invention will now be described but in no way limited with reference to the following Examples.

25 Example 1

Preparation of Bis-trimethylsilyl Methyl Hydroquinone

30 Methyl hydroquinone (27.53g) and hexamethyldisilazane (48.42g) were refluxed together in toluene (400ml) for 2 hours. The resultant bis-trimethylsilyl hydroquinone (75g) was isolated by vacuum distillation.

Preparation of Bis-trimethylsilyl Adipic Acid

Adipic acid (36.54g) and hexamethyldisilazane (48.42g) were refluxed in toluene (400ml) for 4 hours. The resultant bis-
5 trimethylsilyl adipate (84g) was isolated by vacuum distillation.

Terephthaloyl chloride (4.06g), bis-trimethylsilyl methyl-
hydroquinone (4.3g), bis-trimethylsilyl dodecanedioate (1.5g) and
benzyltriethylammonium chloride (0.01g) were weighed under
10 nitrogen into a glass reaction vessel. The reaction mixture was
heated, with stirring under nitrogen, from 90 °C to 260 °C over a
period of 3 hours after which a vacuum was applied for a further
half-hour. The product was washed with dry tetrahydrofuran, dried
under vacuum at 60 °C and characterised by FTIR spectral analysis,
15 ¹³C-NMR spectral analysis and optical scanning under polarised
light.

Figures 1 and 2, respectively, illustrate the FTIR and NMR
spectra of the polymer. Figure 3 is a monochromatic reproduction of
20 a coloured microphotograph of the polymer demonstrating the liquid
crystalline properties of the polymer. The micrograph was taken
between cross polars whilst the polymer was molten. The coloured
region (textured region X shown in Figure 3) is evidence of a
birefringent fluid which can only arise if there is molecular order in
25 the liquid, i.e. a liquid crystalline polymer. Also illustrated in Figure 3
are thread-like structures (Y) which are typically associated with
nematic type liquid crystals.

Examples 2 to 5

30 Poly(ester-anhydride)s having the compositions shown in the
following table were prepared in accordance with the method

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described in Example 1. Each polymer exhibited thermotropic behaviour (viz. a liquid crystalline phase in the polymer melt).

Example	Monomer Ratio		
	50 mole%	40 mole%	10 mole%
2	T	M	A
3	T	M	Su
4	T	M	Se
5	T	P	D

- T: Terephthaloyl Chloride ✓
M: Bis-trimethylsilyl methylhydroquinone
P: Bis-trimethylsilyl phenylhydroquinone
A: Bis-trimethylsilyl adipate
Su: Bis-trimethylsilyl suberate
Se: Bis-trimethylsilyl sebacate
D: Bis-trimethylsilyl dodecanedioate

5

Example 6

The method of Example 1 was used to prepare a poly(ester-anhydride) comprised of residues derived from 50 mole%
10 terephthaloyl chloride, 37.5 mole% bis-trimethylsilyl hydroquinone and 12.5 mole% bis-trimethylsilyl dodecanedioate.

A disc of the polymer material was immersed in deionized water, maintained at room temperature, for one month. The
15 structure was analysed by infrared spectroscopy to investigate hydrolysis of the anhydride linkage. The FTIR spectra of the original polymer (Curve A) and the degraded polymer (Curve B) is shown in Figure 4 where it will be seen that the strong absorption band near

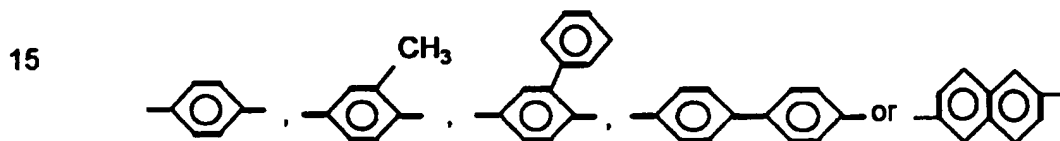
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1790 cm^{-1} for Curve A has almost disappeared at that point in Curve
B.

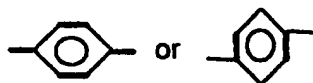
CLAIMS

1. A biodegradable polymer comprising repeating units of an aromatic mesogenic moiety, a hydrolysable moiety and a spacer moiety.
2. A polymer as claimed in claim 1 in which the mesogenic moiety comprises aromatic ester residues.
3. A polymer as claimed in claim 1 or claim 2 in which the mesogenic moiety comprises residues of the general formula:

$$\text{OC} - \text{R}_2 - \text{CO} - \text{O} - \text{R}_1 - \text{O} - \text{R}_2 - \text{CO}$$
in which R_1 is:



and R_2 is

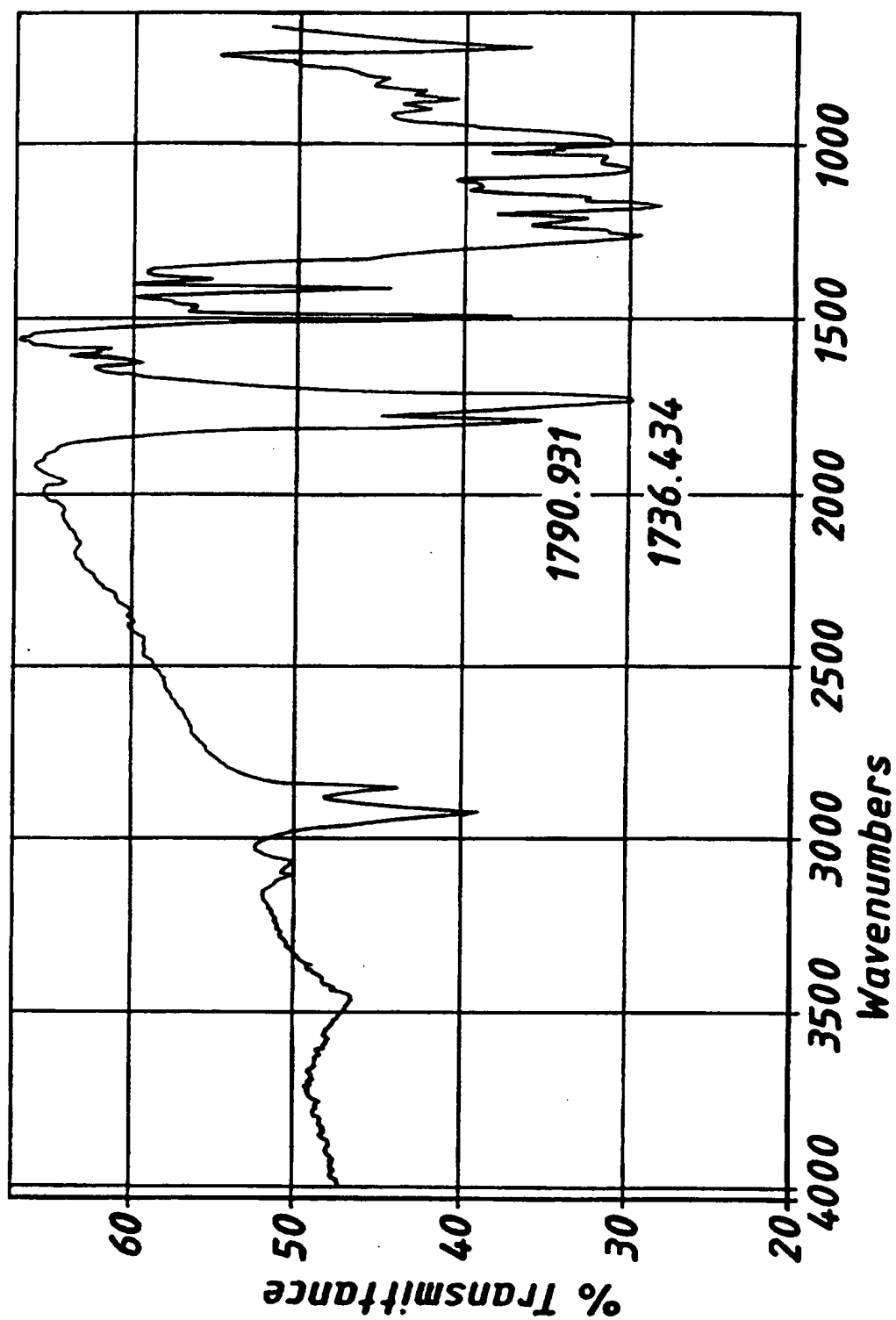


4. A polymer as claimed in any one of the preceding claims in which the hydrolysable moiety comprises anhydride linkages.
5. A polymer as claimed in any one of the preceding claims in which the hydrolysable moiety comprises residues of mixed aromatic-aliphatic anhydride.
6. A polymer as claimed in any one of the preceding claims formed by the condensation of aromatic and aliphatic diacids or functional derivatives thereof with a nucleophilic compound.

7. A polymer as claimed in claim 6 in which the nucleophilic compound is an aromatic diol or thiol.
- 5 8. A polymer as claimed in any one of the preceding claims having repeating units if the general formula:
9.
$$\left[\left(-OC-R_2-CO-O-R_1-O \right)_x \right] \left(OC-R_2-CO-O-OC-(CH_2)_n-COO \right)_y$$
in which n is an integer from 2 to 20; R₁ and R₂ are as defined in claim 3 and the ratio of x:y is from 1:99 to 99:1,
- 10 10. A medical fixation device comprising a biodegradable polymer as defined in any one of the preceding claims.
- 15 11. A device as claimed in claim 10 comprising a prosthesis or a bone filling material.

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FIG. 1.



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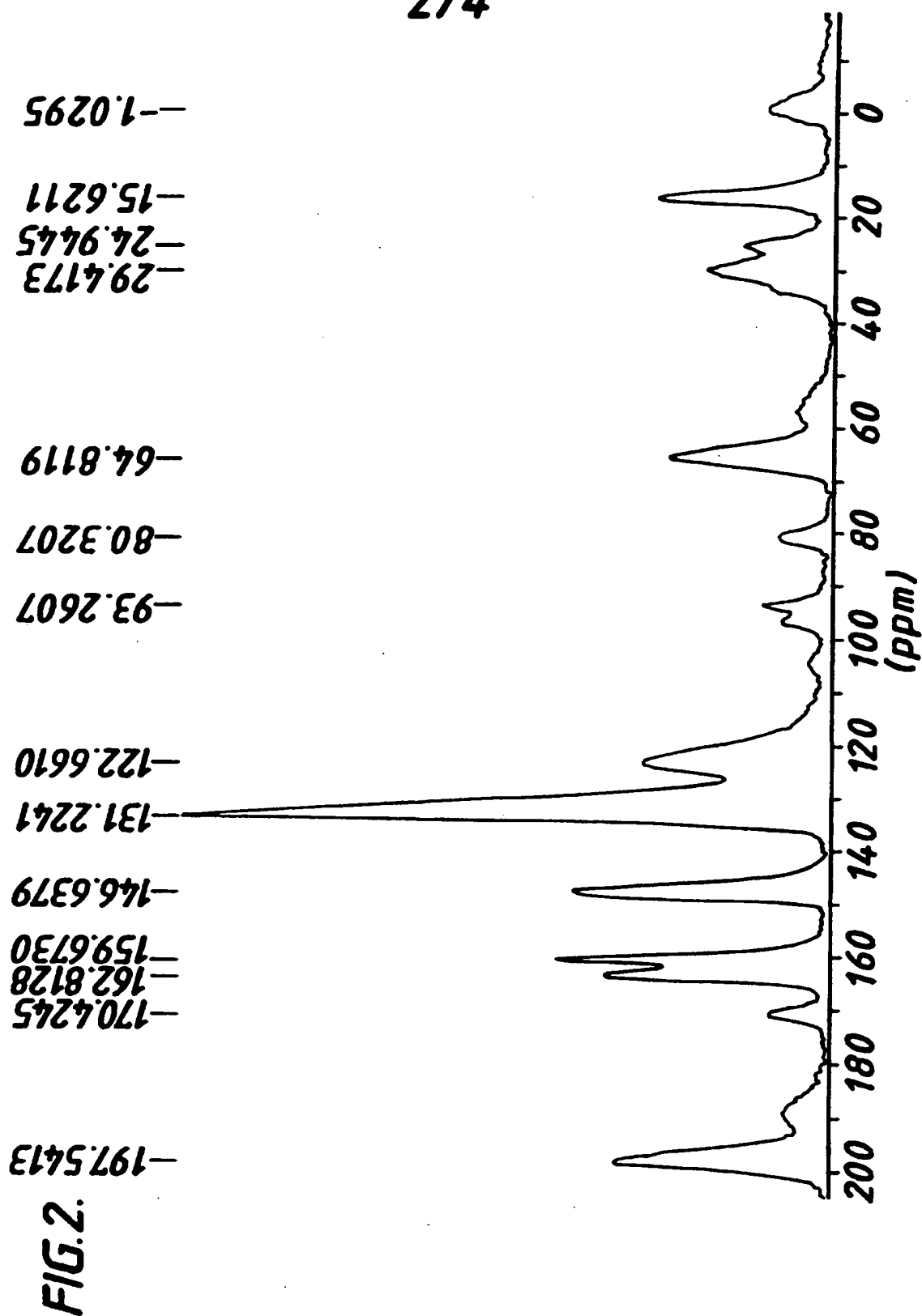


FIG. 2.

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FIG. 3.

Temp = 305.2°C

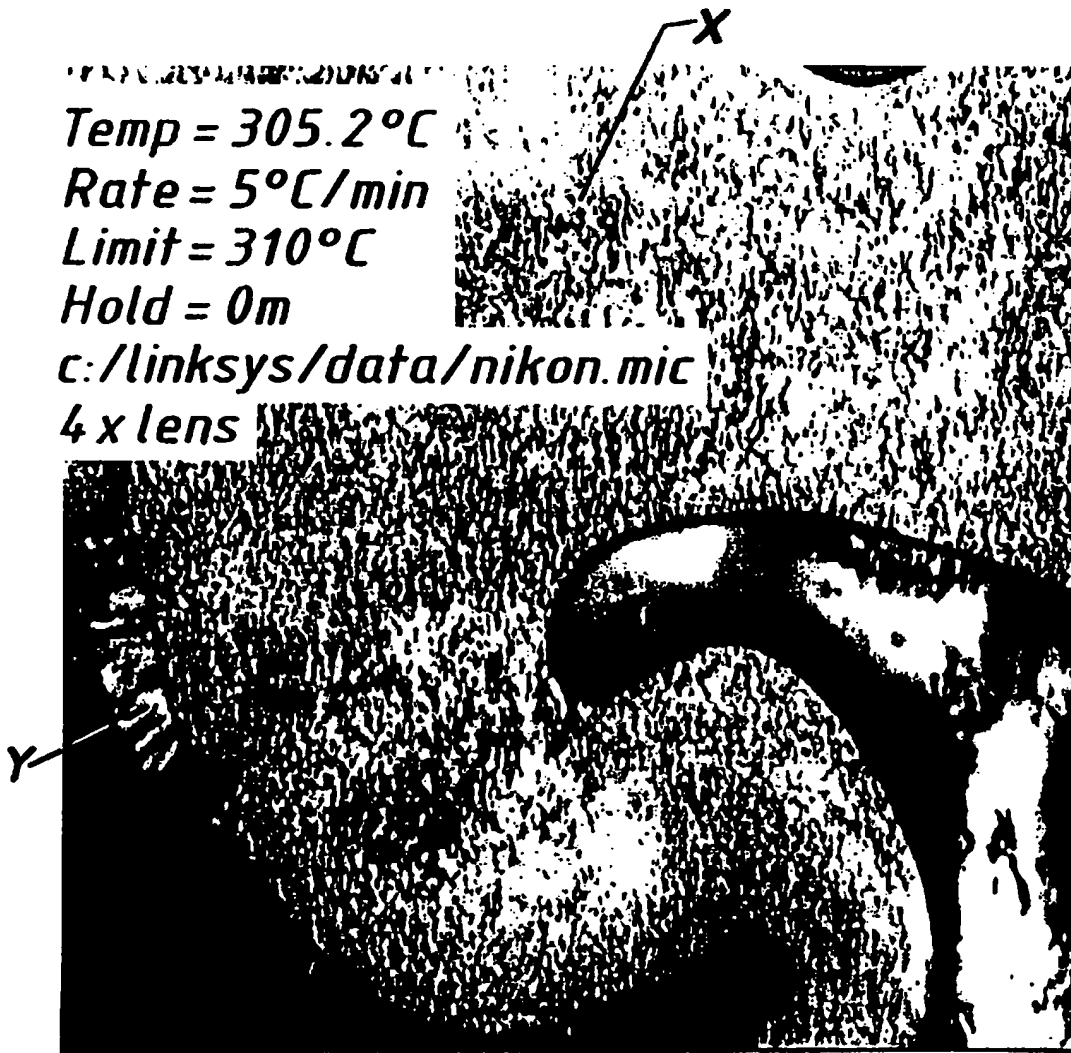
Rate = 5°C/min

Limit = 310°C

Hold = 0m

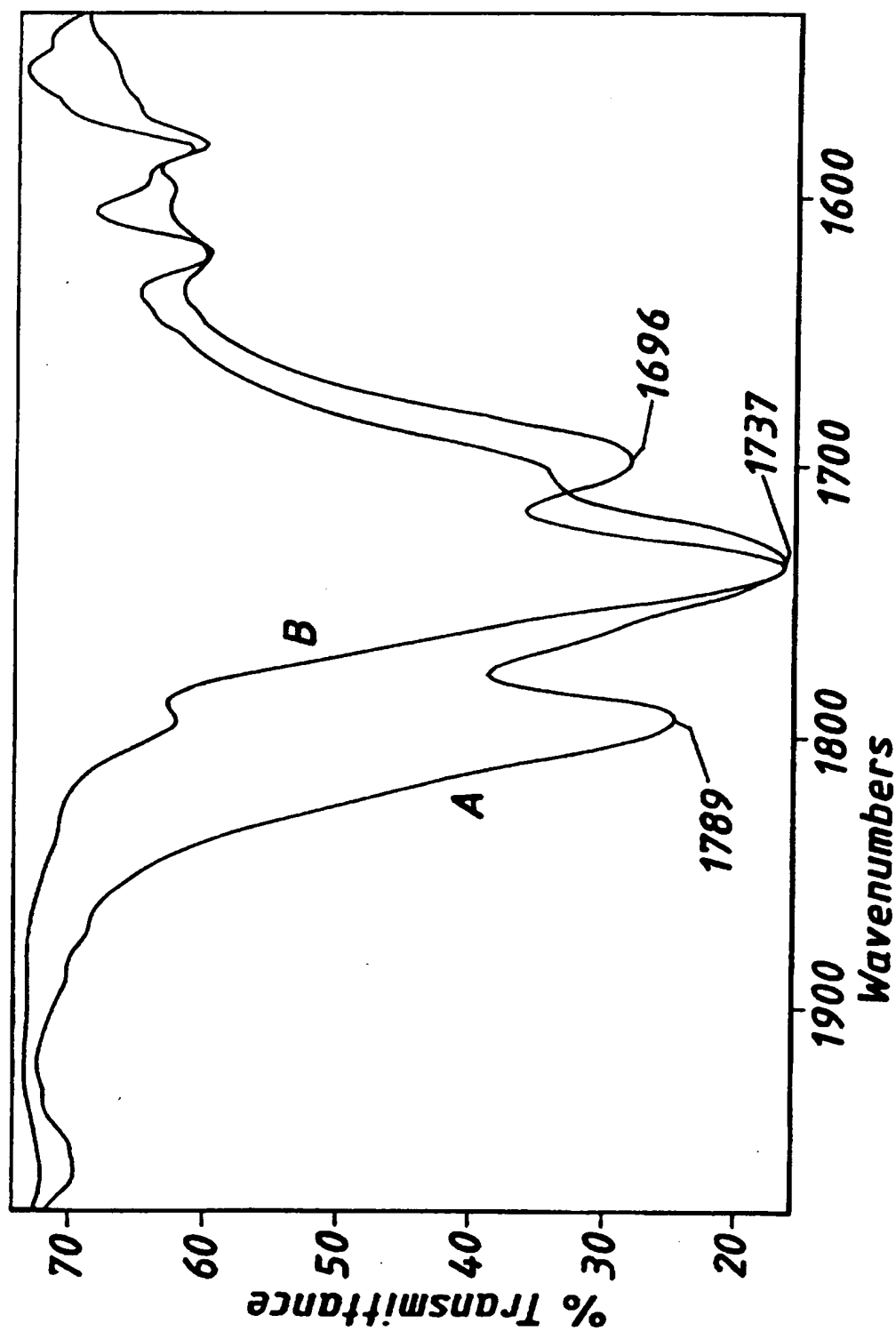
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4x lens



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FIG. 4.



INTERNATIONAL SEARCH REPORT

Intern. Appl. No.
PCT/GB 97/01586

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C09K19/38 C08G67/04 A61L25/00 A61L27/00

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Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C08G C09K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MACROMOLECULES, vol. 28, no. 14, 3 July 1995, pages 4785-4794, XP000517421 XIAOMING JIN ET AL: "SYNTHESIS, CHARACTERIZATION, AND IN VITRO DEGRADATION OF A NOVEL THERMOTROPIC TERNARY COPOLYESTER BASED ON P-HYDROXYBENZOIC ACID, GLYCOLIC ACID, AND P-HYDROXYCINNAMIC ACID"	1,2,10
Y	see the whole document ---	11
Y	EP 0 636 639 A (ETHICON INC) 1 February 1995 see claims 1-10 see page 7, line 3 - line 48 ---	11
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 246 341 A (MASSACHUSETTS INST TECHNOLOGY) 25 November 1987 see abstract; claims 1,2; example 3 see page 9, line 10 - line 18 ---	1,4,5, 10,11
A	EP 0 350 127 A (STAMICARBON) 10 January 1990 see claims 1-6 ---	11
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 97/01586

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